F ENT COOPERATION TREA

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 14 November 2000 (14.11.00)	
International application No. PCT/EP00/02031	**Applicant's or agent's file reference** PF3623/WO
International filing date (day/month/year) 09 March 2000 (09.03.00)	**Priority date** (day/month/year) 11 March 1999 (11.03.99)
Applicant COSTE, Herve, Jean-Clement et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

09 October 2000 (09.10.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Manu Berrod

Telephone No.: (41-22) 338.83.38

For receiving Office use only

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty

International Application No PCT/EP 00/02031

International Filing Date 09 MAR 2000 (09.03.00)

EUROPEAN PATENT OFFICE
PCT INTERNATIONAL APPLICATION
Name of receiving Office and "PCT Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* PF3623/WO

Box No. I TITLE OF INVENTION

Expression

Box No. II APPLICANT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below).*

Glaxo Group Limited
Glaxo Wellcome House
Berkeley Avenue
Greenford, Middlesex, UB6 0NN
GB

☐ This person is also inventor.

Telephone No. 0171 493 4060

Facsimile No. 0181 966 8838

Teleprinter No. 25456

State *(i.e. country)* of nationality: GB

State *(i.e. country)* of residence: GB

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTORS

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

COSTE, Herve Jean-Clement
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Centre de Recherches Glaxo Courtaboeuf
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France

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality: FR

State *(i.e. country)* of residence: FR

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country).*

REES, Marion L
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UB6 0NN
GB

Telephone No.: 0171-493-4060

Facsimile No.: 0181-966-8838

Teleprinter No.: 25456

☐ Mark this check-box where no agent or common representative is indicated and the address below is used instead to indicate a special address to which correspondence should be sent.

Express Mail Label No.: EL395942773US

PCT/EP 00/02031

Sheet No ....2...

Continuation of Box No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTORS

If none of the following sub-boxes is used, this sheet is not to be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

ELLIS, Jonathan Henry
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SG1 2NY
GB

This person is:

- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality: GB

State *(i.e. country)* of residence: GB

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:

- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality:

State *(i.e. country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:

- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality:

State *(i.e. country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:

- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality:

State *(i.e. country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes; at least one must be marked)*:

Regional Patent

- ☑ **AP** **ARIPO Patent:** **GH** Ghana, **GM** Gambia, **KE** Kenya, **LS** Lesotho, **MW** Malawi, **SD** Sudan, **SZ** Swaziland, **UG** Uganda, **ZW** Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ☑ **EA** **Eurasian Patent:** **AM** Armenia, **AZ** Azerbaijan, **BY** Belarus, **KG** Kyrgyzstan, **KZ** Kazakstan, **MD** Republic of Moldova, **RU** Russian Federation, **TJ** Tajikistan, **TM** Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☑ **EP** **European Patent:** **AT** Austria, **BE** Belgium, **CH and LI** Switzerland and Liechtenstein, **CY** Cyprus, **DE** Germany, **DK** Denmark, **ES** Spain, **FI** Finland, **FR** France, **GB** United Kingdom, **GR** Greece, **IE** Ireland, **IT** Italy, **LU** Luxembourg, **MC** Monaco, **NL** Netherlands, **PT** Portugal, **SE** Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☑ **OA** **OAPI Patent:** **BF** Burkina Faso, **BJ** Benin, **CF** Central African Republic, **CG** Congo, **CI** Côte d'Ivoire, **CM** Cameroon, **GA** Gabon, **GN** Guinea, **GW** Guinea Bissau, **ML** Mali, **MR** Mauritania, **NE** Niger, **SN** Senegal, **TD** Chad, **TG** Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)*.....

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

- ☑ **AE** United Arab Emirates
- ☑ **AL** Albania.....
- ☑ **AM** Armenia.....
- ☑ **AT** Austria.....
- ☑ **AU** Australia.....
- ☑ **AZ** Azerbaijan
- ☑ **BA** Bosnia and Herzegovina .....
- ☑ **BB** Barbados
- ☑ **BG** Bulgaria.....
- ☑ **BR** Brazil.....
- ☑ **BY** Belarus.....
- ☑ **CA** Canada
- ☑ **CH and LI** Switzerland and Liechtenstein
- ☑ **CN** China.....
- ☑ **CU** Cuba.....
- ☑ **CZ** Czech Republic.....
- ☑ **DE** Germany.....
- ☑ **DK** Denmark.....
- ☑ **EE** Estonia.....
- ☑ **ES** Spain.....
- ☑ **FI** Finland.....
- ☑ **GB** United Kingdom
- ☑ **GD** Grenada
- ☑ **GE** Georgia.....
- ☑ **GH** Ghana.....
- ☑ **GM** Gambia
- ☑ **HR** Croatia .....
- ☑ **HU** Hungary.....
- ☑ **ID** Indonesia
- ☑ **IL** Israel.....
- ☑ **IN** India.....
- ☑ **IS** Iceland
- ☑ **JP** Japan.....
- ☑ **KE** Kenya.....
- ☑ **KG** Kyrgyzstan.....
- ☑ **KP** Democratic People's Republic of Korea.....
- ☑ **KR** Republic of Korea.....
- ☑ **KZ** Kazakstan.....
- ☑ **LC** Saint Lucia
- ☑ **LK** Sri Lanka
- ☑ **LR** Liberia
- ☑ **LS** Lesotho.....
- ☑ **LT** Lithuania
- ☑ **LU** Luxembourg
- ☑ **LV** Latvia
- ☑ **MD** Republic of Moldova.....
- ☑ **MG** Madagascar.....
- ☑ **MK** The former Yugoslav Republic of Macedonia
- ☑ **MN** Mongolia
- ☑ **MW** Malawi.....
- ☑ **MX** Mexico.....
- ☑ **NO** Norway
- ☑ **NZ** New Zealand.....
- ☑ **PL** Poland.....
- ☑ **PT** Portugal.....
- ☑ **RO** Romania
- ☑ **RU** Russian Federation.....
- ☑ **SD** Sudan
- ☑ **SE** Sweden
- ☑ **SG** Singapore
- ☑ **SI** Slovenia.....
- ☑ **SK** Slovakia.....
- ☑ **SL** Sierra Leone
- ☑ **TJ** Tajikistan.....
- ☑ **TM** Turkmenistan.....
- ☑ **TR** Turkey.....
- ☑ **TT** Trinidad and Tobago.....
- ☑ **UA** Ukraine.....
- ☑ **UG** Uganda.....
- ☑ **US** United States of America.....
- ☑ **UZ** Uzbekistan.....
- ☑ **VN** Viet Nam.....
- ☑ **YU** Yugoslavia.....
- ☑ **ZA** South Africa
- ☑ **ZW** Zimbabwe

Check-boxes reserved for designating States which have become party to the PCT after issuance of this sheet.

- ☑ **CR** Costa Rica.....
- ☑ **DM** Dominica.....
- ☑ **MA** Morocco.....
- ☑ **TZ** Tanzania.....

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)*

Box No. VI PRIORITY CLAIM ☐ Further priority claims are indicated in the Supplemental Box

Filing Date of Earlier Application (day/month/year)	Number of earlier application	Where earlier application is: national application: country	regional application:* regional Office	international application: receiving Office
item (1) 11 March 1999 (11.03.99)	9905498.3	GB		
item (2)				
item (3)				

☐ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office)* identified above as item(s): _____

** Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earli application was filed (Rue 4.10(b)(ii)). See Supplemental Box.*

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

ıice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):* ISA/

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority):* Date *(day/month/year)* Number Country *(or regional office)*

Box. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following **number of sheets:**

request	3
description (excluding sequence listing part)	27
claims	5
abstract	1
drawings	10
sequence listing part of description	
Total number of sheets	46

This international application is **accompanied by** the item(s) marked below:

1. ☒ fee calculation sheet
2. ☐ separate signed power of attorney
3. ☐ copy of general power of attorney; reference number, if any:
4. ☐ statement explaining lack of signature
5. ☐ priority document(s) identified in Box No. VI as item(s):
6. ☐ translation of international application into (language):
7. ☐ separate indications concerning deposited microorganism or other biological material
8. ☐ nucleotide and/or amino acid sequence listing in computer readable form
9. ☐ other *(specify):*

Figure of the drawings which ould accompany the abstract:

Language of filing of the international application: English

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

Marion Rees

Marion L Rees
Agent for the Applicants

For receiving Office use only

1. Date of actual receipt of the purported international application: 0 9 MAR 2000 (09. 03. 2000)
2. Drawings ☒ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:
4. Date of timely receipt of the required corrections under PCT Article 11(2):
5. International Searching Authority specified by the applicant: ISA/
6. ☐ Transmittal of search copy delayed until search fee is paid

For International Bureau use only

Date of receipt of the record copy by the International Bureau

See Notes to the request form

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
PF3623/WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/02031	09/03/2000	11/03/1999
International Patent Classification (IPC) or national classification and IPC C12N15/85		
Applicant GLAXO GROUP LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 5 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
09/10/2000	20.06.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Giebeler, K Telephone No. +49 89 2399 8546

Form PCT/IPEA/409 (cover sheet) (January 1994)

Express Mail Label No.:
EL395942773US

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/02031

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-27	as originally filed				

Claims, No.:

1-34	as received on	11/05/2001	with letter of	10/05/2001	

Drawings, sheets:

1/10-10/10	as originally filed

Sequence listing part of the description, pages:

1-4, filed with the letter of 05.04.2000

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☒ furnished subsequently to this Authority in written form.
   - ☒ furnished subsequently to this Authority in computer readable form.
   - ☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 1-34 (all partially).

because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 1-34 (all partially).

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-8,19,24,28-34
	No:	Claims	9-18,20-23,25-27
Inventive step (IS)	Yes:	Claims	1-8,19,24,28-34
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-17,25,26,28-31
	No:	Claims	18-24,27,32-34 (see below)

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
se separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. This preliminary examination is being carried out **only** on subject-matter for which an international search report has been established, i.e. subject-matter relating to the sequence of the human hsp70 gene encoding the 5' untranslated region of the human hsp70 mRNA. Therefore, the subject-matter of claim 1(c) relating to other sequences and claims 2-34 when dependent on or referring to claim 1(c) has not been subject to preliminary examination.

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

2. The following documents are cited:

D2: WO 87 00861 A
D3: WO 94 11521 A
D4: DATABASE GENEMBL [Online] 16 July 1988 (1988-07-16) HUNT,C. AND MORIMOTO, R.I.: 'Human heat shock protein (hsp 70) gene, complete cds' & HUNT, C. AND MORIMOTO, R.I.: ' PROC. NATL. ACAD. SCI. USA, vol. 82, no. 19, 1985, pages 6455-6459
D6: PITTO LETIZIO ET AL: PLANT PHYSIOLOGY, vol. 100, no. 4, 1992, pages 1827-1833
D7: US-A-5 659 122
D10: JOSHI CHANDRASHEKHAR P ET AL: NUCLEIC ACIDS RESEARCH, vol. 23, no. 4, 1995, pages 541-549

3. NOVELTY

The present application is based on the finding that the 5' untranslated region of the human hsp70 gene acts as a translational enhancer to express a heterologous polypeptide even in the absence of the human hsp70 promoter.
It is stated in claim 1 that the claimed DNA molecule (i) does not encode a

mammalian Hsp70 and (ii) does not comprise an hsp promoter.

Although claims 9-18, 20-23 and 25-27 directly or indirectly refer to claim 1, they include the possibility of other DNA molecules being present, due to the use of the term "comprising". The vector of claim 9, for instance, "comprises" a DNA molecule according to claims 1 to 7, but may also "comprise" any other DNA molecule such as the human hsp70 promoter or gene. The same applies to the expression systems of claims 10 to 15 which may also "comprises" human hsp70 the gene or promoter. Therefore, claims 9-18, 20-23 and 25-27 are considered to lack novelty over the prior art.

The document D2 discloses recombinant DNA molecules comprising inter alia the 5' untranslated region of a human hsp70 clone, see especially page 10, paragraph 3 and page 15, paragraph 3. D2 is thus prejudicial to the novelty of claims 9-17 and 25-27.
The document D3 relates mainly to the DNA of the bovine hsp70A promoter but also suggests the use of the human hsp70 5' untranslated region in the expression of various antigens such as vaccine antigens (see especially p. 14, l. 14 - p. 15, l. 22; p. 16, l. 30 - p. 17, l. 22; p. 23, l. 1-16; p. 23, l. 24 - p. 24, l. 19). D3 is thus prejudicial to the novelty of claims 9-17, 20 and 25-27.
The document D4 discloses the sequence of the 5' noncoding leader sequence of 212 nucleotides of the human hsp70 gene and is thus prejudicial to the novelty of claims 9-17, 25 and 26.
The expression systems of claims 10-15 encompass any expression system based on human cells which naturally "comprises" the 5' untranslated region of the hsp70 gene. These claims and also claims 16 and 17 thus lack novelty. Since any human cell comprises the hsp70 5'untranslated region, claims 18 and 20-23 also lack novelty. Claims 25-27 lack novelty accordingly.

4. INVENTIVE STEP

4.1. The subject-matter of claims 1-8, 19, 24 and 28-34 is considered to involve an inventive step since it could not be expected from any of the prior art documents D2, D3, D4, D6, D7 or D10 that the 5' untranslated region of the human hsp70 gene would act independently as a translational enhancer to express a

heterologous polypeptide even in the absence of the human hsp70 promoter. The document D10, which appears to be particularly relevant, suggests the role of the 5' untranslated leader sequence of eukaryotic mRNAs encoding heat shock proteins in selective translation, and Table 1 of D10 refers to the human hsp70 5' untranslated region. However, the Applicant's argumentation that it could not be expected from D10 that the sequence could be used in the absence of the homologous promoter to express a heterologous polypeptide, could be followed.

4.2. It should be noted that claim 18 as far as it relates to the use of the vector according to claim 9 is not considered to involve an inventive step since it would have been obvious for a person skilled in the art faced with the problem of treating a deficiency in the expression of a polypeptide to use a regulatory molecule as disclosed in D2, D3 or D4 by operably linking it with a sequence encoding a deficient polypeptide.

5. INDUSTRIAL APPLICABILITY

For the assessment of the present claims 18-24, 27 and 32-34 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VIII

Certain observations on the international application

6. Claim 13 defines a product in terms of processes for its preparation, which is only considered to be clear if there is no other information available in the application which could enable the applicant to define the product satisfactorily by reference to its composition, structure or other testable parameters.
Claim 30 is unclear because it defines a product be reference to a process of administration.

Claims

1. A DNA molecule that can be transcribed to provide an RNA molecule having an untranslated region that provides an increased efficiency of translation of a polypeptide when operably linked to a region encoding said polypeptide; wherein said DNA molecule

(i) does not encode a mammalian Hsp70;
(ii) does not comprise an hsp promoter; and
(iii) comprises

a) the sequence:
5'ataacggctagcctgaggagctgctgcgacagtccactacctttttcgagagtgactcccgttgtcccaaggcttccc agagcgaacctgtgcggctgcaggcaccggcgcgtcgagtttccggcgtccggaaggaccgagctcttctcgcgg atccagtgttccgtttccagcccccaatctcagagccgagccgacagagagcagggaaccgc-3',

b) the complement of the sequence given in a), or

c) a sequence having substantial sequence identity with a sequence as defined in a) or b) above.

2. A DNA molecule according to claim 1; wherein said untranslated region is a 5' untranslated region.

3. A DNA molecule according to claim 1 or 2 wherein said untranslated region has a ΔG of below -10 kCal/mol.

4. A DNA molecule according to any preceding claim wherein said sequence has a ΔG that is below -30 kCal/Mol.

5. A DNA molecule according to any preceding claim wherein said sequence has a ΔG that is below -40 kCal/Mol.

6. A DNA molecule according to any preceding claim wherein said untranslated region has a ΔG of below -50 kCal/Mol.

7. A DNA molecule according to any preceding claim wherein expression of said polypeptide is heat shock responsive.

8. An RNA molecule obtainable by transcribing a DNA molecule according to any of claims 1 to 7.

9. A vector comprising a DNA molecule according to any of claims 1 to 7.

10. An expression system comprising a DNA molecule according to any of claims 1 to 7 or a vector according to claim 9.

11. An expression system according to claim 10 which comprises one or more cells.

12. An expression system according to claim 11 comprising one or more eukaryotic cells.

13. An expression system according to claim 11 comprising one or more mammalian cells.

14. An expression system according to claim 11 comprising one or more human cells.

15. An expression system according to claim 10 which is a cell free expression system.

16. A method of obtaining a polypeptide comprising expressing the polypeptide using an expression system according to any of claims 10 to 15 and, optionally, purifying the polypeptide.

17. A method according to claim 16 comprising the step of providing the expression system with a heat shock.

18. A method of treating a deficiency in the expression of a polypeptide, comprising providing a patient with a DNA molecule as claimed in any of claims 1 to 7 which encodes said polypeptide, a vector as claimed in claim 9 comprising said DNA molecule, or a cell comprising said DNA molecule or vector.

19. A method of treating a deficiency in the expression of a polypeptide, comprising providing a patient with a DNA molecule as claimed in any one of claims 1 to 7 wherein said molecule is provided in a manner to allow it to become operably linked with a sequence already present in the patient which encodes said polypeptide.

20. A method of treating a disorder (e.g. an infection) treatable by providing an increased immune response, comprising providing a patient with a vaccine comprising a DNA molecule as claimed in any of claims 1 to 7 or a vector as claimed in claim 9.

21. A method according to claim 18 or 19; wherein a DNA molecule or vector is provided under conditions allowing it to integrate within the patient's genome.

22. A method according to claim 18; wherein a cell is provided under conditions allowing it to be maintained within the patient.

23. A method according to claim 22 wherein said cell is a cell that has been removed from the patient and has been modified prior to being reintroduced to the patient.

24. A method of treating a deficiency in the expression of a polypeptide, comprising providing the patient with an RNA molecule as claimed in claim 8.

25. A pharmaceutically acceptable composition comprising a DNA molecule according to any of claims 1 to 7, an RNA molecule according to claim 8, or a cell as described in any of claims 11 to 14.

26. A vaccine comprising a DNA molecule according to any of claims 1 to 5, or a vector according to claim 9.

27. The use of a DNA molecule according to any of claims 1 to 7, of an RNA molecule according to claim 8, of a vector according to claim 9, or of an expression system according to any of claims 10 to 15, in achieving increased expression of a polypeptide.

28. A DNA molecule according to any one of claims 1 to 7 for use in therapy.

29. A DNA molecule according to claim 28 for use in therapeutic or prophylactic vaccination.

30. A DNA molecule according to claim 28 or 29 when administered by particle bombardment.

31. A DNA molecule according to claim 28, 29 or 30 for use in achieving an increased immune response.

32. Method of therapeutic or prophylactic vaccination comprising administering an effective amount of a DNA molecule as claimed in any one of claims 1 to 7.

33. Method according to claim 32 wherein the DNA molecule is administered by particle bombardment.

34. Method according to claim 32 or 33 for use in achieving an increased immune response.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
PF3623/WO		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 00/02031	09/03/2000	11/03/1999
Applicant		
GLAXO GROUP LIMITED		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

[ ] contained in the international application in written form.

[ ] filed together with the international application in computer readable form.

[X] furnished subsequently to this Authority in written form.

[X] furnished subsequently to this Authority in computer readble form.

[X] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[X] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

[ ] the text is approved as submitted by the applicant.

[X] the text has been established by this Authority to read as follows:

METHOD TO IMPROVE TRANSLATION OF POLYPEPTIDES BY USING UNTRANSLATED REGIONS FROM HEAT-SHOCK PROTEINS

5. With regard to the **abstract**,

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. 14

[ ] as suggested by the applicant.

[X] because the applicant failed to suggest a figure.

[ ] because this figure better characterizes the invention.

[ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 00/02031

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/85 C12N5/10 A61K48/00 C07K14/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS, WPI Data, PAJ, MEDLINE, BIOTECHNOLOGY ABS, SCISEARCH, EMBASE, CHEM ABS Data, STRAND, GENSEQ, EMBL

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HUNT C R ET AL: "Inducible expression of cDNAs in a vector based upon the mouse HSP70 heat-shock promoter;" J.CELL.BIOCHEM.; SUPPL.12D, 260, 1988, XP000933846 abstract --- WO 87 00861 A (BATTELLE MEMORIAL INSTITUTE) 12 February 1987 (1987-02-12) page 15, paragraph 3 figure 2C page 10, paragraph 3 claims 1,8,13 --- -/--	1-41 d 36 - 41: DNA vacc. of a murine herpes
X		1,2,6, 12-23, 31-34

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 August 2000	07/09/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	ALCONADA RODRIG.., A

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Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 94 11521 A (BIOSTAR INC) 26 May 1994 (1994-05-26) cited in the application page 14, line 14 -page 15, line 22 page 16, line 30 -page 17, line 23 page 23, line 1-16 page 23, line 24 -page 24, line 19	1,3,4,6, 12-23, 26,31-41
X	DATABASE GENEMBL 'Online! 16 July 1988 (1988-07-16) HUNT,C. AND MORIMOTO, R.I.: "Human heat shock protein (hsp 70) gene, complete cds" XP002144203 cited in the application Accession M11717 -& HUNT, C. AND MORIMOTO, R.I.: "Conserved features of eukaryotic hsp-70 genes revealeed by comparison with the nucleotide sequence of human hsp-70" PROC. NATL.ACAD. SCI. USA, vol. 82, no. 19, 1985, pages 6455-6459, XP000929693 figure 2	1-23,31, 32,34
X	MOSELEY POPE L ET AL: "Heat stress regulates the human 70-kDa heat-shock gene through the 3'-untranslated region." AMERICAN JOURNAL OF PHYSIOLOGY, vol. 264, no. 6 PART 1, 1993, pages L533-L537, XP000925808 ISSN: 0002-9513 figure 4	1-5, 12-23, 31-34
A	PITTO LETIZIO ET AL: "Role of the leader sequence during thermal repression of translation in maize, tobacco, and carrot protoplasts." PLANT PHYSIOLOGY (ROCKVILLE), vol. 100, no. 4, 1992, pages 1827-1833, XP000929495 ISSN: 0032-0889 figures 1,3 page 1829, right-hand column -page 1830, left-hand column table 1	1-41
A	US 5 659 122 A (AUSTIN GLENN DOUGLAS) 19 August 1997 (1997-08-19) see EXAMPLE	1-41

-/--

4

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	HESS MARK A ET AL: "Sequence and structure determinants of Drosophila Hsp70 mRNA translation: 5'-UTR secondary structure specifically inhibits heat shock protein mRNA translation." NUCLEIC ACIDS RESEARCH, vol. 24, no. 12, 1996, pages 2441-2449, XP002144202 ISSN: 0305-1048 cited in the application the whole document	1-41
A	LIARAKOS CHARLES D ET AL: "The translation efficiency of ovalbumin mRNA is determined in part by a 5'-end hairpin structure." ARCHIVES OF BIOCHEMISTRY AND BIOPHYSICS, vol. 315, no. 1, 1994, pages 54-59, XP000925807 ISSN: 0003-9861 page 55, right-hand column, paragraph 4 -page 56, right-hand column, paragraph 2; figure 2	1-41
A	JOSHI CHANDRASHEKHAR P ET AL: "5' untranslated leader sequences of eukaryotic mRNAs encoding heat shock induced proteins." NUCLEIC ACIDS RESEARCH, vol. 23, no. 4, 1995, pages 541-549, XP000929506 ISSN: 0305-1048 figures 1,2; tables 2,3	1-41

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-41 relate to a product by reference to a desirable characteristic or property, namely, to a DNA molecule that can be transcribed to provide an RNA having an untranslated region that provides an increased efficency of translation of a polypeptide when operably linked to a region encoding said polypeptide. The claims cover all products having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such products. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the product by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the sequence of the human hsp70 gene encoding for the 5'-untranslated region of the human hsp70 mRNA.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 00/02031

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 8700861 A	12-02-1987	AU 604214 B	13-12-1990
		AU 6286086 A	05-03-1987
		EP 0231368 A	12-08-1987
		ES 2003085 A	16-10-1988
		NO 871328 A	30-03-1987
		ZA 8605702 A	25-03-1987
WO 9411521 A	26-05-1994	US 5521084 A	28-05-1996
		CA 2148492 A	26-05-1994
		EP 0672156 A	20-09-1995
		JP 8505283 T	11-06-1996
		US 5981224 A	09-11-1999
		US 5733745 A	31-03-1998
US 5659122 A	19-08-1997	US 5362865 A	08-11-1994
		AU 7833494 A	22-03-1995
		CA 2169854 A	09-03-1995
		EP 0716709 A	19-06-1996
		WO 9506742 A	09-03-1995

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 00/02031

Box I Observations where certain claims w re f und unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 24-30 and 39-41 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid. specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
C12N 15/85, 5/10, A61K 48/00

A2

(11) International Publication Number: WO 00/53785

(43) International Publicati n Date: 14 September 2000 (14.09.00)

(21) International Application Number: PCT/EP00/02031

(22) International Filing Date: 9 March 2000 (09.03.00)

(30) Pri rity Data:
9905498.3 11 March 1999 (11.03.99) GB

(71) Applicant *(for all designated States except US)*: GLAXO GROUP LIMITED [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: COSTE, Herve, Jean–Clement [FR/FR]; Laboratoire Glaxo Wellcome, Centre de Recherches Glaxo Courtaboeuf, Z.A. de Courtaboeuf, 25, avenue de Quebec, F–91940 Les Ulis (FR). ELLIS, Jonathan, Henry [GB/GB]; Glaxo Wellcome plc, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB).

(74) Agent: REES, Marion, L.; Glaxo Wellcome plc, Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex, UB6 0NN (GB).

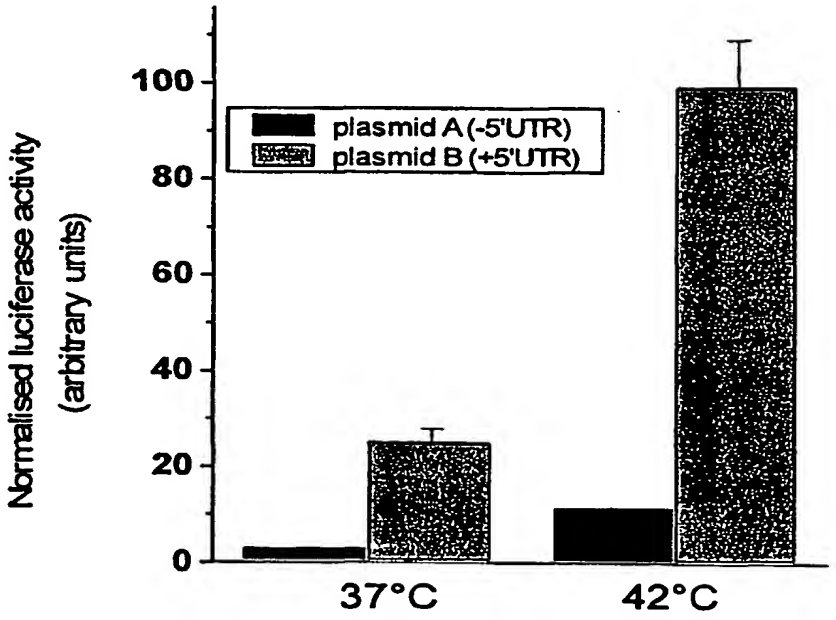
(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
Without international search report and to be republished upon receipt of that report.

(54) Title: EXPRESSION

(57) Abstract

Untranslated regions associated with the heat shock response can be used to obtain increased efficiency of translation of polypeptides that are not necessarily normally associated with the heat shock response. This allows the development of greatly improved expression systems. The invention is also useful, for example, in the treatment of a patient suffering from a deficiency in the expression of a polypeptide and in the provision of vaccines.



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EE	Estonia	**LR**	Liberia	**SG**	Singapore		

Claims

1. A DNA molecule that can be transcribed to provide an RNA molecule having an untranslated region that provides an increased efficiency of translation of a polypeptide when operably linked to a region encoding said polypeptide; wherein said DNA molecule does not encode a mammalian Hsp70.

2. A DNA molecule according to claim 1 that does not comprise the bovine hsp70 promoter.

3. A DNA molecule according to any preceding claim; wherein said untranslated region is at least 175 nucleotides long.

4. A DNA molecule according to any preceding claim; wherein said untranslated region is at least 200 nucleotides long.

5. A DNA molecule according to any preceding claim; wherein said untranslated region is about 215 nucleotides long.

6. A DNA molecule according to any preceding claim; wherein said untranslated region is a 5' untranslated region.

7. A DNA molecule according to any preceding claim, comprising:

a) the sequence:
5'ataacggctagcctgaggagctgctgcgacagtccactacctttttcgagagtgactcccgttgtcccaaggcttccc
agagcgaacctgtgcggctgcaggcaccggcgcgtcgagtttccggcgtccggaaggaccgagctcttctcgcgg
atccagtgttccgtttccagcccccaatctcagagccgagccgacagagagcagggaaccgc-3',

b) the complement of the sequence given in a), or

c) a sequence having substantial sequence identity with a sequence as defined in a) or b) above

8. A DNA molecule according to any preceding claim wherein said untranslated region has a ΔG of below -10 kCal/mol.

9. A DNA molecule according to any preceding claim; wherein said sequence has a ΔG that is below -30 kCal/Mol

10. A DNA molecule according to any preceding claim; wherein said sequence has a ΔG that is below -40 kCal/Mol

11. A DNA molecule according to any preceding claim; wherein said untranslated region has a ΔG of below -50 kCal/Mol

12. A DNA molecule according to any preceding claim; wherein expression of said polypeptide is heat shock responsive.

13. An RNA molecule obtainable by transcribing a DNA molecule according to any of claims 1 to 12.

14. A vector comprising a DNA molecule according to any of claims 1 to 12.

15. An expression system comprising a DNA molecule according to any of claims 1 to 12 or a vector according to claim 14.

16. An expression system according to claim 15 which comprises one or more cells.

17. An expression system according to claim 16 comprising one or more eukaryotic cells.

18. An expression system according to claim 16 comprising one or more mammalian cells.

19. An expression system according to claim 16 comprising one or more human cells

20. An expression system according to claim 15 which is a cell free expression system

21. A method of obtaining a polypeptide comprising expressing the polypeptide using an expression system according to any of claims 15 to 20 and, optionally, purifying the polypeptide.

22. A method according to claim 21 comprising the step of providing the expression system with a heat shock.

23. A polypeptide when obtained via a method according to claim 21 or claim 22.

24. A method of treating a deficiency in the expression of a polypeptide, comprising providing a patient with a DNA molecule as described in any of claims 1 to 12 which encodes said polypeptide, with a vector comprising said DNA molecule, or with a cell comprising said DNA molecule or vector.

25. A method of treating a deficiency in the expression of a polypeptide, comprising providing a patient with a DNA molecule that can be transcribed to provide the untranslated region defined in any of claims 1 to 12; wherein said

molecule is provided in a manner to allow it to become operably liked with a sequence already present in the patient which encodes said polypeptide.

26. A method of treating a disorder (e.g. an infection) treatable by providing an increased immune response, comprising providing a patient with a vaccine comprising a DNA molecule as described in any of claims 1 to 12 or comprising a vector including said DNA molecule.

27. A method according to claim 24 or 25; wherein a DNA molecule or vector is provided under conditions allowing it to integrate within the patient's genome.

28. A method according to claim 24; wherein a cell is provided under conditions allowing it to be maintained within the patient.

29. A method according to claim 28 wherein said cell is a cell that has been removed from the patient and has been modified prior to being reintroduced to the patient.

30. A method of treating adeficiency in the expression of a polypeptide, comprising providing the patient with an RNA molecule according to claim 13 or with a polypeptide according to claim 23.

31. A pharmaceutically acceptable composition comprising a DNA molecule according to any of claims 1 to 12, an RNA molecule according to claim 13, a polypeptide according to claim 23 or a cell as described in any of claims 16 to 19.

32. A vaccine comprising a DNA molecule according to any of claims 1 to 10, or a vector including said DNA molecule.

33. The use of a DNA molecule according to any of claims 1 to 12, of an RNA molecule according to claim 13, of a vector according to claim 14, or of an expression system according to any of claims 15 to 20, in achieving increased expression of a polypeptide.

34. The invention as substantially herein before described with reference to the accompanying drawings and examples.

35. A DNA molecule according to any one of claims 1 to 12 for use in therapy.

36. A DNA molecule according to claim 35 for use in therapeutic or prophylactic vaccination.

37. A DNA molecule according to claim 35 or 36 when administered by particle bombardment.

38. A DNA molecule according to claim 35, 36 or 37 for use in achieving an increased immune response.

39. Method of therapeutic or prophylactic vaccination comprising administering an effective amount of a DNA molecule as claimed in any one of claims 1 to 12.

40. Method according to claim 39 wherein the DNA molecule is administered by particle bombardment.

41. Method according to claim 39 or 40 for use in achieving an increased immune response.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
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(43) International Publication Date
14 September 2000 (14.09.2000)

PCT

(10) International Publication Number
WO 00/53785 A3

(51) International Patent Classification[7]: C12N 15/85, 5/10, A61K 48/00, C07K 14/48

(21) International Application Number: PCT/EP00/02031

(22) International Filing Date: 9 March 2000 (09.03.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
9905498.3 11 March 1999 (11.03.1999) GB

(71) Applicant *(for all designated States except US)*: **GLAXO GROUP LIMITED** [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

(72) Inventors; and
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(74) Agent: REES, Marion, L.; Glaxo Wellcome plc, Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex, UB6 0NN (GB).

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Published:
— *With international search report.*

(88) Date of publication of the international search report:
25 January 2001

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 00/53785 A3

(54) Title: METHOD TO IMPROVE TRANSLATION OF POLYPEPTIDES BY USING UNTRANSLATED REGIONS FROM HEAT-SHOCK PROTEINS

(57) Abstract: Untranslated regions associated with the heat shock response can be used to obtain increased efficiency of translation of polypeptides that are not necessarily normally associated with the heat shock response. This allows the development of greatly improved expression systems. The invention is also useful, for example, in the treatment of a patient suffering from a deficiency in the expression of a polypeptide and in the provision of vaccines.

INTERNATIONAL SEARCH REPORT

Inte .ional Application No
PCT/EP 00/02031

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/85 C12N5/10 A61K48/00 C07K14/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS, WPI Data, PAJ, MEDLINE, BIOTECHNOLOGY ABS, SCISEARCH, EMBASE, CHEM ABS Data, STRAND, GENSEQ, EMBL

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HUNT C R ET AL: "Inducible expression of cDNAs in a vector based upon the mouse HSP70 heat-shock promoter;" J.CELL.BIOCHEM.; SUPPL.12D, 260, 1988, XP000933846 abstract --- WO 87 00861 A (BATTELLE MEMORIAL INSTITUTE) 12 February 1987 (1987-02-12) page 15, paragraph 3 figure 2C page 10, paragraph 3 claims 1,8,13 --- -/--	1-41 1,2,6, 12-23, 31-34

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 August 2000	07/09/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	ALCONADA RODRIG.., A

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INTERNATIONAL SEARCH REPORT

Int. .tional Application No
PCT/EP 00/02031

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 94 11521 A (BIOSTAR INC) 26 May 1994 (1994-05-26) cited in the application page 14, line 14 -page 15, line 22 page 16, line 30 -page 17, line 23 page 23, line 1-16 page 23, line 24 -page 24, line 19	1,3,4,6, 12-23, 26,31-41
X	DATABASE GENEMBL 'Online! 16 July 1988 (1988-07-16) HUNT,C. AND MORIMOTO, R.I.: "Human heat shock protein (hsp 70) gene, complete cds" XP002144203 cited in the application Accession M11717 -& HUNT, C. AND MORIMOTO, R.I.: "Conserved features of eukaryotic hsp-70 genes revealeed by comparison with the nucleotide sequence of human hsp-70" PROC. NATL.ACAD. SCI. USA, vol. 82, no. 19, 1985, pages 6455-6459, XP000929693 figure 2	1-23,31, 32,34
X	MOSELEY POPE L ET AL: "Heat stress regulates the human 70-kDa heat-shock gene through the 3'-untranslated region." AMERICAN JOURNAL OF PHYSIOLOGY, vol. 264, no. 6 PART 1, 1993, pages L533-L537, XP000925808 ISSN: 0002-9513 figure 4	1-5, 12-23, 31-34
A	PITTO LETIZIO ET AL: "Role of the leader sequence during thermal repression of translation in maize, tobacco, and carrot protoplasts." PLANT PHYSIOLOGY (ROCKVILLE), vol. 100, no. 4, 1992, pages 1827-1833, XP000929495 ISSN: 0032-0889 figures 1,3 page 1829, right-hand column -page 1830, left-hand column table 1	1-41
A	US 5 659 122 A (AUSTIN GLENN DOUGLAS) 19 August 1997 (1997-08-19) see EXAMPLE	1-41

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INTERNATIONAL SEARCH REPORT

Int. .tional Application No
PCT/EP 00/02031

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	HESS MARK A ET AL: "Sequence and structure determinants of Drosophila Hsp70 mRNA translation: 5'-UTR secondary structure specifically inhibits heat shock protein mRNA translation." NUCLEIC ACIDS RESEARCH, vol. 24, no. 12, 1996, pages 2441-2449, XP002144202 ISSN: 0305-1048 cited in the application the whole document	1-41
A	LIARAKOS CHARLES D ET AL: "The translation efficiency of ovalbumin mRNA is determined in part by a 5'-end hairpin structure." ARCHIVES OF BIOCHEMISTRY AND BIOPHYSICS, vol. 315, no. 1, 1994, pages 54-59, XP000925807 ISSN: 0003-9861 page 55, right-hand column, paragraph 4 -page 56, right-hand column, paragraph 2; figure 2	1-41
A	JOSHI CHANDRASHEKHAR P ET AL: "5' untranslated leader sequences of eukaryotic mRNAs encoding heat shock induced proteins." NUCLEIC ACIDS RESEARCH, vol. 23, no. 4, 1995, pages 541-549, XP000929506 ISSN: 0305-1048 figures 1,2; tables 2,3	1-41

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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-41 relate to a product by reference to a desirable characteristic or property, namely, to a DNA molecule that can be transcribed to provide an RNA having an untranslated region that provides an increased efficency of translation of a polypeptide when operably linked to a region encoding said polypeptide. The claims cover all products having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such products. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the product by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the sequence of the human hsp70 gene encoding for the 5'-untranslated region of the human hsp70 mRNA.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. .tional Application No
PCT/EP 00/02031

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